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Research Article

FORMULATION AND EVALUATION OF LANSOPRAZOLE DELAYED RELEASE PELLETS

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ABSTRACT

Proton pump inhibitors are acid labile drugs. These drugs will degrade in acidic environment of stomach and will lead to therapeutic inefficacy. It is necessary to bypass the acidic ph of the stomach, which can be achieved by formulating delayed release dosage forms (single unit or multiple units) by using different enteric polymers. The aim of the present study was to develop a pharmaceutically equivalent, stable, cost of effective and quality improved formulation of lansoprazole enteric coated pellets [delayed release]. The formulation process was carried out in FBP by solution -suspension layering technique and comparing it with marketed dosage form. The preparation contains nine formulations by drug loading, sub coating, enteric coating, and lubrication steps. The prepared batches oflansoprazole enteric coated pellet can be evaluated forApi Characterization likesolubility, water content, loss on drying bulk density, tapped density, carr's index, hausner`s ratio, angle of repose, melting point and particle size distribution and evaluation of delayed release formulations like assay, acid resistance, dissolution (in acid stage followed by buffer stage), content uniformity, average net fill content, and friability. E8 enteric coated pellets were found to be optimum and were filled into capsules. These capsules were evaluated and the results were found to be more similar with innovator.

Keywords: Delayed Release Pellets**,** Fluid Bed processor, Active pharmaceutical ingredient.

INTRODUCTION

Delayed release systems release a bolus of the drug after a predetermined time in a predetermined location, i.e. they do not release the drug immediately after ingestion, for example enteric-coated tablets, pulsatile-release capsules

Delayed release dosage forms[1] are designed to provide spatial placement or temporal targeted delivery of a drug to the distal human gut. Spatial placement relates to targeting a drug to a specific organ or tissue, while temporal delivery refers to desired rate of drug release to target tissue over a specified period of treatment.
The primary aim of using delayed release products is to protect the drug from gastric fluids, to reduce gastric distress caused by drugs particularly irritating to thestomach or to facilitate gastrointestinal transit for drugs that are better absorbed from intestine
The drugs contained in such a system are those that are:

- Destroyed in the stomach or by intestinal enzymes
- Known to cause gastric distress
- Absorbed from a specific intestinal site or

- Meant to exert local effect at a specific gastrointestinal site

Delayed release products are typically enteric-coated or targeted to the colon .The two types of delayed release systems are:

- Intestinal release systems
- Colonic release system

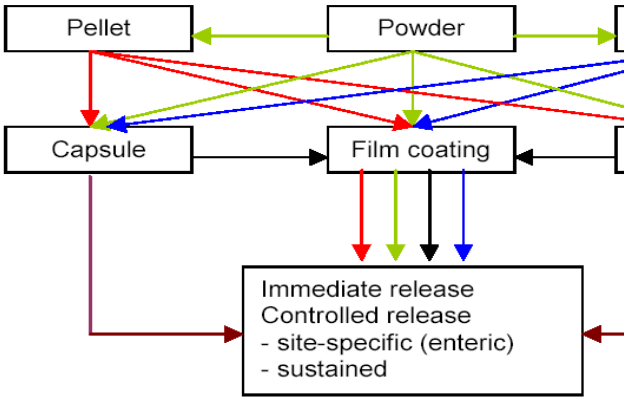


Fig. 1: Delayed release solid oral dosage forms[2]

PELLETS[3]

Pharmaceutical pellets are agglomerates of fine powder particles or bulk drugs and excipients, small, free-flowing, spherical or semi-spherical solid units, size ranges from about 0.5mm to 1.5mm (ideal size for oral administration) , obtained from diverse starting materials utilizing different processing techniques and conditions.

Applications of Pellets

Pellets have varied applications in a number of industries and an innovative use of its could achieve maximum profitability. Some of the few instances where smooth surfaced uniform pellets are being successfully used are highlighted below:

- Improved aesthetic appearance of products.
- Controlled release rate by coating with desired polymers.
- Larger surface area of pellets enables better distribution, dissolution andabsorption.
- Chemically incompatible products can be delivered in single dosage form by encapsulation.
- Avoid powder dusting in chemical industries.
- Varied applications are possible e.g., Sustained release detergent powder, milkshake pellets.
- Ensures improved flow properties and flexibility in formulation development and manufacture.
- Colouring of coating material gives distinction of beads of different thickness, making it easy for blending in desired proportions.

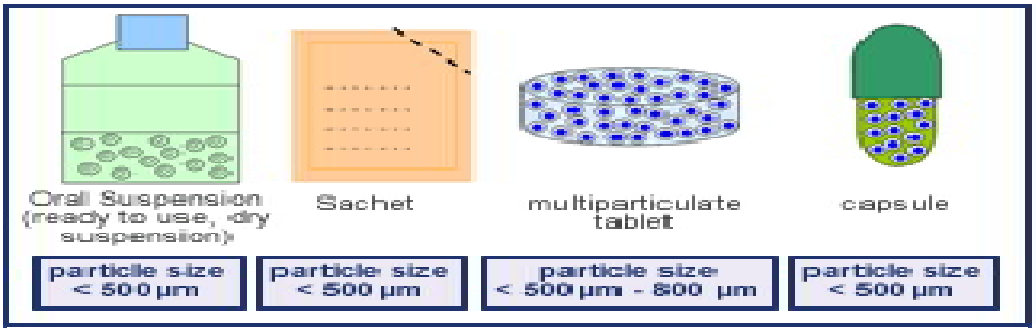


Fig.2:Flexibility of pellets in development of dosage form

Desirable properties of pellets[4]

1. Uncoated pellets

- Uniform spherical shape and smooth surface
- Optimum size, between 600 and 1000 m
- Improved flow characteristics
- High physical strength and integrity
- Good hardness and low friability
- High bulk density
- Ease and superior properties for coating
- Reproducible packing of beds and columns.

2. Coated pellets

- Contain as much as possible of the active ingredient to keep the size of the final dosage form within reasonable limits
- Have desired drug release characteristics.

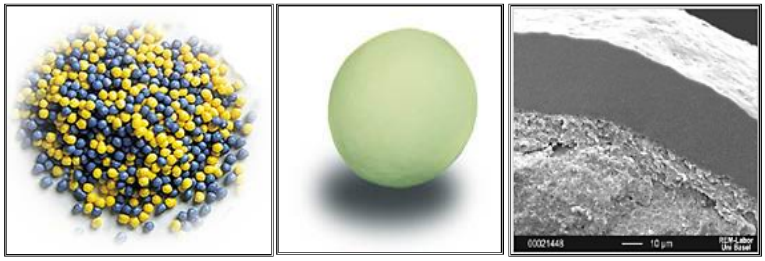


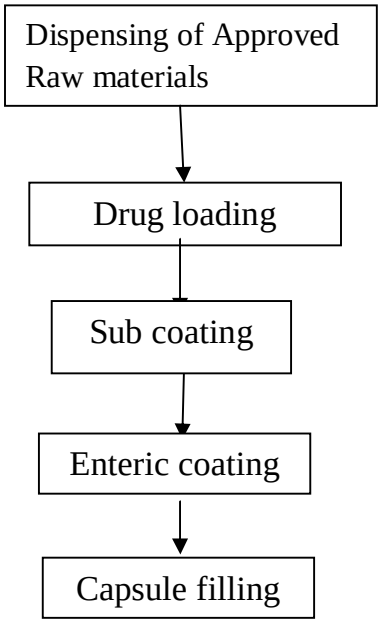
Fig. 3: (a) Pellets, (b) Perfect pellet, (c) Coated pellet

MATERIALS AND METHODS

Lansoprazole was obtained as a gift sample from Hetero drugs, Hyd. Sugar spheres from Werner, L-Hydroxypropyl cellulose Gift sample from Aqualon, Methacrylic acid copolymer type C was obtained as a gift sample from Degussa, Polyethylene glycol from Clariant. All other chemicals used were of pharmaceutical grade.

FORMULATION METHOD[5]

Sequence of Events Done During Formulation



1. Screening

- Required quantity of sugar spheres (sugar spheres USP-NF) were sifted through mesh #20.
- Mesh #20 passed sugar spheres were sifted through mesh #25 and retains were collected.

2. Drug Coating

➢ **Preparation of Drug Suspension**

- HPC (LH 31) was dissolved in Purified water, and was under continuous stirring till clear solution was formed.
- Now sucrose was added under continuous stirring.
- L-HPC (L Type) was added to above solution under continuous stirring to get uniform dispersion. Remaining quantity of water was added to above solution
- Corn starch and Heavy magnesium carbonate were added to above solution and stirred for 20 minutes to get uniform dispersion.
- Lansoprazole was slowly added and the stirring was continued for 30 minutes (or) till a uniform suspension was formed.
- Finally SLS was added to the above solution

3. Sub Coating (Barrier Coating)

➢ **Preparation of Sub coating dispersion**

- HPC was dissolved in purified water and stirred to get a clear solution.
- Sucrose was added to the above solution and stirred.
- LHPC was added to above solution and remaining quantity of purified water was added to the solution and stirred for 20min.
- Now corn starch was added to above solution and stirred to get a uniform dispersion.

4. Enteric coating

➢ **Preparation of Enteric coating Dispersion**

- Purified water was taken in a stainless steel vessel. Methacrylic acid copolymer was slowly added to the purified water and the contents were mixed for 30 minutes under continuous stirring.
- TEC was taken in to a beaker and purified water was added and mixed for 5 minutes. Now Polysorbate 80 was added to the solution under continuous stirring.
- Talc was added to above solution and stirred to get uniform dispersion.
- Solution of the above step was added slowly to first step under continuous stirring and mixed for about 30 minutes.
- The dispersion obtained was sifted through mesh #100 and collected in a stainless steel vessel.

5. Lubrication

- Specified quantity of talc, colloidal silicon dioxide were taken, added to enteric coated pellets and lubricated.

FORMULATION TRAILS

Table1:Formula for Drug Coating

S. No	DRUG COATING	D1	D2	D3	D4	D5	D6
1	Sugar Spheres (#20/#25)	150	150	150	150	**150**	150
2	Lansoprazole	30	30	30	30	**30**	30
3	Sucrose	20	20	20	20	**20**	20
4	Magnesium Carbonate (Light)	22.4	22.4	22.4	22.4	**-**	-
5	Magnesium Carbonate (Heavy)	-	-	-	-	**22.4**	22.4
6	Corn Starch	5	5	5	5	**5**	5
7	L-HPC (LH31)	20	20	27	27	**27**	27
8	HPC(LH-11)	-	-	-	3	**3**	-
9	SLS	8.6	8.6	8.6	8.6	**8.6**	8.6
10	Povidone	5	10	10	-	**-**	-
11	HPMC	-	-		-	**-**	3
12	Water	q.s	q.s	q.s	q.s	q.s	q.s

	Total	261	266	273	266	**266**	266
	% Drug Content	80	82.4	86.4	91.5	**99.5**	95.3
	% Yield	75	80	84	90	**97**	82

Table 2:Formulas for Sub Coating

S.NO	SUB COATING	D5S1	D5S2	D5S3	D5S4	D5S5
1	Drug Pellets	266	266	266	**266**	266
2	Pharma Grade Sugar	30	30	30	**30**	30
3	Corn Starch	-	-	5	**5**	10
4	L-HPC(LH31)	10	10	10	**10**	10
5	HPC(L Type)	1	-	1	**2**	2
6	HPMC	-	1	-	**-**	**-**
7	Water	q.s	q.s	q.s	**q.s**	q.s
8	Total	307	307	312	**313**	318
9	%yield	87	88	90	**98**	85

Table 3:Formulas for Enteric Coating

S.NO	ENTERIC COATING	D5 S1E1	D5 S1E2	D5 S3E3	D5 S3E4	D5 S4E5	D5 S4E6	D5 S4E7	D5 S4E8	D5 S4E9
	% of Enteric coating	***10%***	***15%***	***10%***	***15%***	***10%***	***15%***	***15%***	***17%***	***19%***
1	**Sub Coated Pellets**	307	307	312	312	313	313	313	313	313
2	**Eudragit L30D55**	24.75	37.13	25.14	37.74	25.25	37.86	37.86	42.9	47.98
3	**Tri- ethyl Citrate**	2.475	3.713	2.514	3.774	2.525	3.786	-	4.29	4.798
4	**Polyethylene Glycol**	-	-	-	-	-	-	3.786	-	-
5	**Talc**	2.979	4.448	3.027	4.5208	3.0275	4.5502	4.5502	5.152	5.732
6	**Polysorbate 80**	0.495	0.741	0.501	0.753	0.505	0.757	0.757	0.858	0.959
7	**Purified Water**	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
	Total	337.7	353.05	343.2	358.8	344.3	359.95	359.95	366.21	372.47

API CHARACTERIZATION[6]

1. Description

The appearance of API was examined by visual observation. Lansoprazole isa white to brownish white colored powder.

2. Solubility

Solubility of drug is an important physico- chemical property because it affects the bio- availability of drug and the rate of drug release into the dissolution medium.

Lansoprazole is freely Soluble in DMF and insoluble in water.

3. Water Content (by Karl-Fisher)

Water Content Should is between 4.5% and 6.7%.

4. LOD

Loss on drying is determined by IR moisture analyzer, at 105^0C.2gms of sample was placed in analyzer and observed until required temperature was attained. Then loss on drying was determined.

5. a) Bulk Density[7]

Apparent bulk density (P_b) was determined by pouring blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated by using the following formula

$$P_b = M / V_b$$

Where, P_b = Bulk Density
M = Weight of sample in gm
V_b = Final volume of blend in cm^3

b) Tapped Density[7]

It is the ratio of total mass of the powder to the tapped volume of powder. The volume was measured by tapping the powder for 500 times. Then the tapping was done for 750 times and the tapped volume was noted. The tapped density was calculated by using the following formula

$$P_t = M / V_t$$

P_t = Tapped Density
M = Weight of the sample in gm
V_t = Tapped volume of blend in cm^3

c) Angle of Repose (θ)[7]

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose.

$$\tan\theta = h/r$$
$$\theta = \tan^{-1}(h/r)$$

Where,
θ is the angle of repose
H is height of pile
r is radius of the base of pile
Different ranges of flow ability in terms of angle of repose are given in Table

Table: 4 Relationship between Angle of repose (θ) and flow properties

Angle of Repose(θ)(degree)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

d) Compressibility Index and Hausners ratio[7]

The compressibility index and the Hausner ratio are determined by measuring both the bulk density and tapped density of a powder.
Basic methods for the determination of compressibility Index and Hausner Ratio
While there are some variations in the method of determining the compressibility index and Hausner ratio, the basic procedure is to measure the unsettled apparent volume (V_b), and the final tapped volume (V_t), of the powder. The compressibility index and the Hausner ratio are calculated as follows.

$$\% \text{ Compressibility (Carr's index)} = \frac{\text{Tapped density - Initial bulk density}}{\text{Tapped density}} \times 100$$

Hausner Ratio

$$V_b/V_t \text{ or } \rho_t/\rho_b.$$

Hauser's Ratio is indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

$$\text{Compressibility Index} = 100 \times \text{Tapped density} / \text{Bulk density}$$
$$\text{Hausner Ratio} = \text{Tapped density} / \text{Bulk density}$$

In a variation of these methods, the rate of consolidation is sometimes measured rather than, or in addition to, the change in volume that occurs on tapping. For the compressibility index and the Hausner ratio. The values are placed in the table.

Table 5: Compressibility Index and the Hausner Ratio

Compressibility Index (%)	Flow Character	Hausner Ratio
1 – 10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 – 20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	s1.35 – 1.45
32 – 37	Very Poor	1.46 – 1.59
> 38	Very, Very Poor	> 1.60

6. Melting Point

Melting point was determined using melting point apparatus. The sample was placed in apparatus and observed for the temperature at which the drug melts. The melting of drug was determined to be 166^{0}C.

7. Particle size distribution

This practice was done for the pellets obtained after functional coating to check average size of the pellets. 100 gms of the pellets are shifted in to sieve shaker where a series of sieves was placed (#16, #22, # 25 and #30). The machine was run for 5 minutes, all the meshes were taken out and retained granules were collected by respective mesh and the % retention of pellets by that mesh was calculated. Average particle size was determined. A graph was plotted taking average particle size on X – axis and percent weight undersize on Y – axis.

EVALUATION OF DELAYED RELEASE FORMULATIONS[8]

ASSAY (by HPLC)

Assay: 90-110% (USP)

Chemicals and Reagents

- Triethyl Amine : AR grade
- NaOH : AR grade
- Ortho phosphoric acid : AR grade
- Acetonitrile : HPLC grade
- Water : Milli-Q- grade

Chromatographic Conditions

- Column : Zorbax SBC_{18}, 4.6 X 250 mm, 5µm
- Flow Rate : 1.0ml/min
- Wave length : 285nm
- Injection Volume : 10µl
- Column temp : Ambient
- Run time : 30 minutes.

Preparation of Sample Solution

- Weighed and emptied 20 capsules.
- Accurately weighed and transferred pellets equivalent to 300mg of Lansoprazole into a 100ml flask.
- About 60ml of diluent A was added to the flask &sonicated for 20min with occasional shaking till pellets were dissolved.(bath temperature :20 -25^{o}C).
- 20ml of acetonitrile and 20ml of internal standard solution was added to the above solution and centrifuged at 5000 rpm for 10minutes.
- 4ml of the clear supernatant was collected and diluted to 100ml with diluents B
- The solution was filtered through 0.45µm membrane.

Procedure

10 µl of mobile phase, standard solution (5 times) and sample solution were separately injected into HPLC. The chromatograms were recorded and peak responses were measured.

Calculation

$$\% \text{ labelled amount} = \frac{R_T \times W_S \times 25 \times 4 \times 100 \times 100 \times P \times L}{R_S \times 100 \times 50 \times 50 \times W_T \times 4 \times 100 \times T} \times 100$$

R_T= Ratio of peak area of Lansoprazole& internal standard peak in sample solution

R_S=Average ratio of peak area of Lansoprazole& internal standard obtained from 5 replicate injection of standard solution

W_S=Weight of Lansoprazole working standard in mg

W_T=Weight of sample in mg

T =Average fill weight of capsule

P= % Purity of Lansoprazole working standard

L=Label claim of Lansoprazole (mg)

DISSOLUTION (by HPLC) [9]

Acid Stage

Acid stage (Dissolution): NMT 10% of Lansoprazole dissolved in 1hour (USP).

Dissolution Parameters

- Medium : 0.1N HCl
- Volume : 500ml
- Apparatus : USP-II, paddle
- Speed : 75 rpm
- Temp : 37±0.5^{0}C
- Sampling points : 1 hrs.

Chromatographic Conditions

- Column : Zorbax SBC_{18}, 4.6 X 250 mm, 5µm
- Flow Rate : 1.0ml/min
- Wave length: 285nm
- Injection Volume : 10µl
- Column temp : Ambient
- Run time : 15 minute.

Preparation of Sample Solution

- 500ml of 0.1N HCl was transferred into each vessel and allowed the medium to temperature 37±0.5^{0}C.
- One capsule in each vessel was placed and operated at 75 rpm for 1 hour.
- At the end of 1nd hour 0.1N HCl was discarded from each vessel without losing any pellets.
- Entire quantity of pellets of each vessel were transferred immediately into dry individual 100ml volumetric flasks with aid of suitable filter or mesh and ensure complete transfer of pellets to the volumetric flask.
- About 60ml of diluent A was added and sonicated for 20 minutes with shaking until the pellets are completely dissolved.
- Diluted to volume with acetonitrile.
- A portion of solution was filtered through 0.45µ filter and first few ml of filtrate was discarded
- 4ml of above solution was transferred into 100ml volumetric flask and diluted to volume with diluent B.

Procedure

10 µl of blank, standard solution (5 times) and sample solution were separately injected into HPLC. The chromatograms were recorded and peak responses were measured.

Calculation

$$\text{\% labelled amount} = \frac{A_T \times W_S \times P \times 4 \times 100 \times 100}{A_S \times 100 \times 100 \times 100 \times 4 \times L} \times 100$$

A_T=Area of Lansoprazole peak in sample solution
A_S=Average Area of Lansoprazole peak from 5 replicate injection of standard solution
W_S=Weight of Lansoprazole working standard in mg
W_T=Weight of Test in mg
P = % Purity of Lansoprazole working standard
L = Label claim of Lansoprazole

Drug Release (acid stage)

The drug release was calculated by using the following formula

% labeled amount of Lansoprazoledissolved in 0.1N HCL
= % labeled amount of lansp (Assay) - % labeled amount of lansp retained in 0.1NHCL (Acid resistance)

Dissolution (Buffer stage)

Dissolution Parameters

- Medium : pH6.8 sodium phosphate buffer
- Volume : 900ml
- Apparatus :USP-II (paddle)
- Speed : 75 rpm
- Temp : 37±0.5^{0}C
- Sampling points : 10,20,30,45 and 60 min(for profile) ,60min (for single point)

Chromatographic Conditions

- Column : Zorbax SBC_{18}, 4.6 X 250 mm, 5µm
- Flow Rate : 1.0ml/min
- Wave length: 285nm
- Injection Volume : 10µl
- Column temp : Ambient
- Run time : 15 minutes

Preparation of Sample Solution (for single point)

- Proceed as directed under acid stage with a new set of sample from the same batch. After 1 hr 25ml of 0.1N HCl was discarded .425ml of buffer was added to each vessel.PH was adjusted to 6.8 and dissolution was continued to 60min. 10ml of samples were withdrawn from each dissolution vessel. 5ml of the sample solution was immediately transferred into test tubes containing 1ml of 0.25N NaOH in a test tube. The sample was filtered through 0.45µm membrane filter and first few ml of the filtrate was discarded.
- **Preparation of Sample Solution (for profile)**
- Same procedure was followed as directed above for release profile by maintaining the sink conditions. Samples were taken at regular intervals.
- **Procedure:** 10 µl of dissolution medium, standard solution (5 times) and sample solution was separately injected into HPLC. Record the chromatograms and peak responses were measured.

Calculation

$$\text{\% labeled amount dissolved} = \frac{A_T \times W_S \times 5 \times P \times 900 \times 100}{A_S \times 4 \times L \times 100 \times 100 \times 100} \times 100$$

A_T=Area of Lansoprazole peak in sample solution
A_S=Average area of Lansoprazole peak from 5 replicate injection of standard solution
W_S=Weight of Lansoprazole working standard in mg
P=Purity of Lansoprazole working standard
L = Label claim of Lansoprazole

Content Uniformity (HPLC)[10]

Preparation of sample:

Contents of 1 capsule were taken into a 100ml volumetric flask. To this 60ml of diluents A was added and sonicated for 20min with shaking. The above solution was diluted to volume with acetonitrile and mixed. A portion of solution was centrifuged at 5000rpm for 10min.

4ml of clear supernatant solution was diluted to 100ml with diluents B and mixed.

The same procedure was repeated for another 9 capsules.

Procedure& Evaluation

The procedure and evaluation were same as that for the % labeled amount given under the dissolution in acid stage.

Average Net Fill Contents

Weighed 20 intact capsules (W_1), then the contents were removed from each capsule by suitable means and the emptied capsule shells were weighed. Then the net fill content was calculated using formula:

$$\textbf{Average Net Fill Contents (mg)} = \frac{(W_1 - W_2)}{20} \times 100$$

Friability test

Friability is the loss of weight of pellets in the container/package, due to removal of fine particles from the surface. Roche Friabilator was used to measure the friability of the tablets. It was rotated at a rate of 25 rpm. 5 g pellets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the pellets were exposed to rolling, resulting from free fall of pellets within the chamber of the friabilator. After 100 rotations (4 minutes), the pellets were taken out from the friabilator and intact pellets were again weighed collectively after removing fines using sieve # 44 sieve. Permitted percentage friability limit is 0.8%. The percent friability was determined using the following formula.

$$\textbf{Percent friability} = \frac{(W1 - W2)}{W1} \times 100$$

Where

W1 = weight of the pellets before test.

W2 = weight of the pellets after test

RESULTS

Table 6: API CHARACTERIZATIONS

S.No.	TEST	RESULT
1	Description	White to brownish white powder
2	Solubility	Freely Soluble in DMF, insoluble in water.
3	Water Content (by Karl-Fisher)	0.08% w/w
4	LOD	1.83 % w/w
5	Bulk density True density Haussner's Ratio Carr's/Compressibility Index (%)	0.234 gm/ml 0.339 gm/ml 1.42 31%
6	Melting Point	166°C
7	Assay by HPLC	100.4 % w/w
8	Particle Size Analysis	4.6 µm

EVALUATION OF ENTERIC COATED PELLETS

The following results were compared with the Innovator.

Assay

Table 7:Assay of Enteric Coated Pellets

		% Labeled Amount Of Lansoprazole							
INNOVATOR	**E1**	**E2**	**E3**	**E4**	**E5**	**E6**	**E7**	**E8**	**E9**
99.6	99	99	99.1	99.2	99.3	99.2	99.2	99.4	99.1

Acid resistance

Table 8:Acid Resistances of Enteric Coated Pellets

	% labeled amount of Lansoprazole retained in acid								
INNOVATOR	**E1**	**E2**	**E3**	**E4**	**E5**	**E6**	**E7**	**E8**	**E9**
98.9	82	84	83.1	86.2	88.3	93.8	90.2	98.8	99.0

Drug release

Table 9:Drug Release in Acid Stage

	% labeled amount of Lansoprazole released in acid									
Time(hr)	**INNOVATOR**	**E1**	**E2**	**E3**	**E4**	**E5**	**E6**	**E7**	**E8**	**E9**
After 1 hr	**0.7**	17	15	16	13	11	5.4	9	0.5	0.1

Dissolution

Acid stage: 0.1 N HCl, 500ml, paddle, 75rpm, 60 minutes,37±0.5°C.
Buffer stage: pH 6.8 phosphate buffer, 900ml, paddle, 75rpm, 3
Sampling points: 10, 20, 30, 45 and 60 minutes.

Table 10:In Vitro Dissolution in Buffer Stage

Time(min	Innovator	E1	E2	E3	E4	E5	E6	E7	E8	E9
	(% labeled amount dissolved in buffer)									
10	**65**	78.5	76	75.5	73	74.5	70	76	62.5	51
20	**74**	80.5	79	78	75	82	78	85	72	66
30	**80**	80.5	80	85	83	86	82	85	78.5	75
45	**92**	81	82	86	85	88	93	89	91.5	90
60	**95**	81	84	86	88	88	93	90	95	93.5

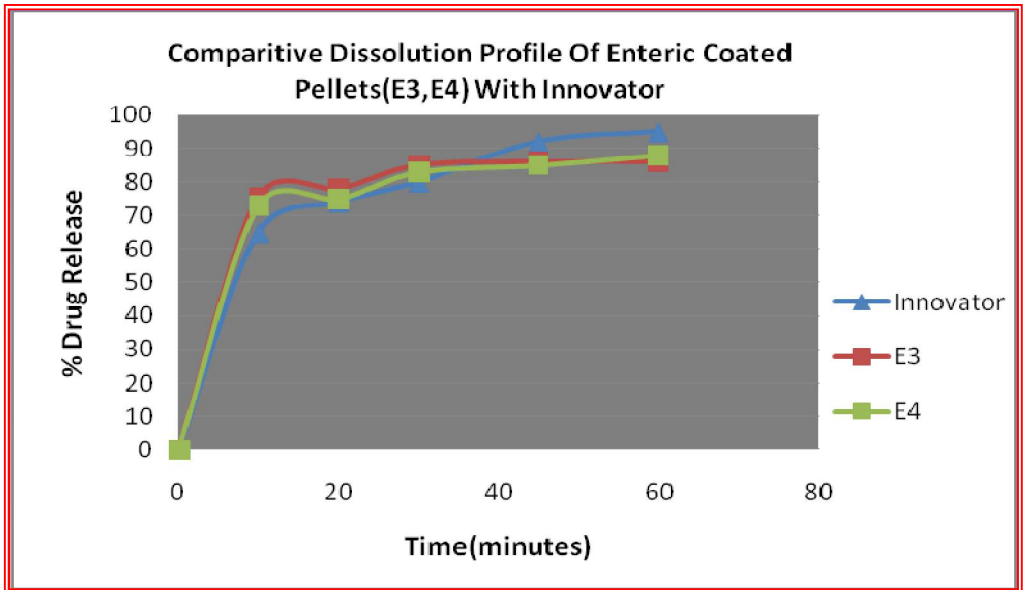


Fig. 4:Invitro Dissolution Profiles of Enteric Coated Pellets (E3, E4) With Innovator

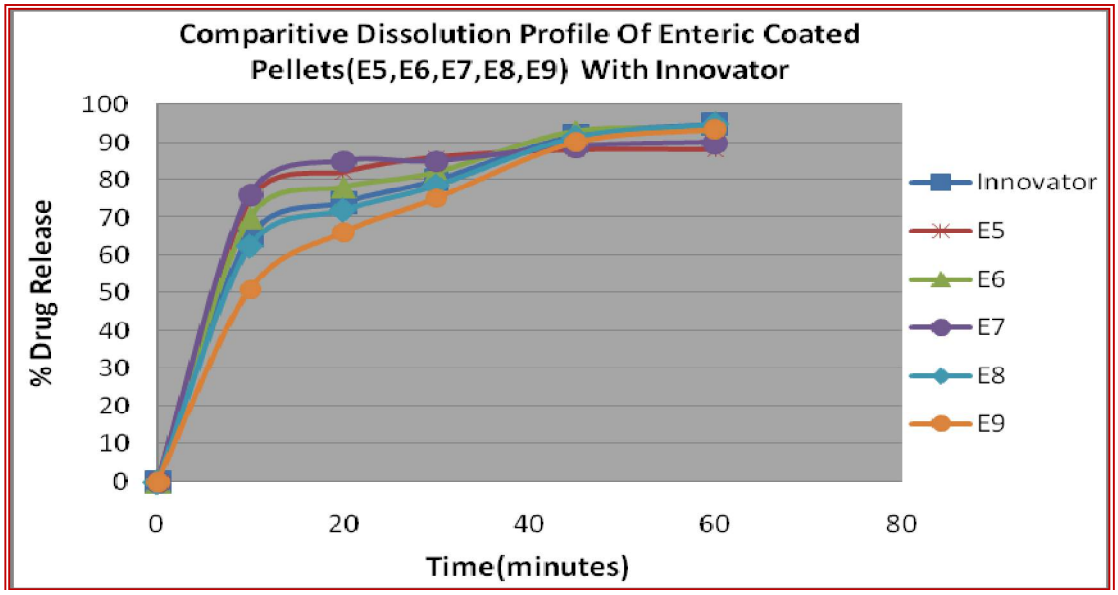


Fig. 5:Invitro Dissolution Profiles of Enteric Coated Pellets (E5, E6, E7, E8 &E9) With Innovator

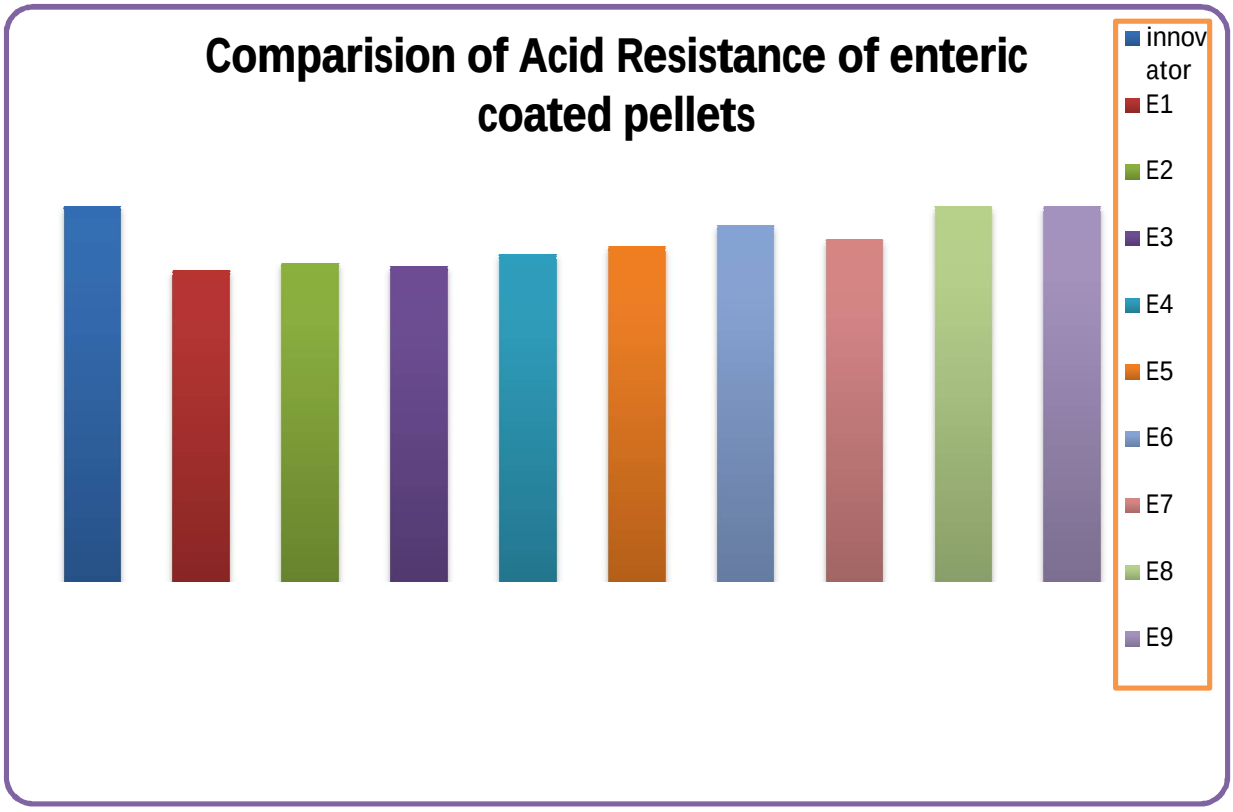


Fig. 6: Comparison of acid resistance of enteric coated pellets with innovator

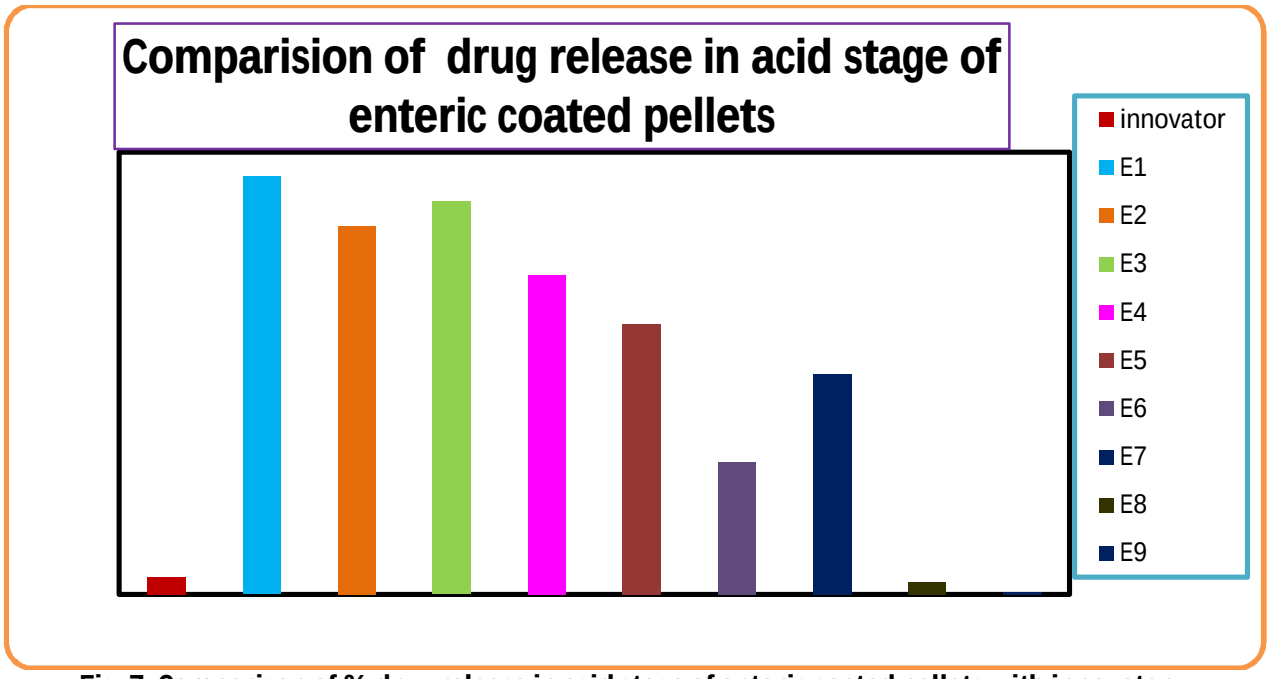


Fig. 7: Comparison of % drug release in acid stage of enteric coated pellets with innovator

EVALUATION STUDIES OF CAPSULES

Enteric coating pellets of formulation E8 were filled into capsules. Evaluation tests were performed for capsules. Then the following parameters were compared with Innovator for evaluation.

Table11:Evaluation of Capsule Formulation

Parameters	Capsule formulation
Assay (%)	99.4
Acid resistance (%)	98.8
Drug Release in acid stage (%)	0.5
Average Net Fill Content	384.092

ContentUniformity

The assay values for different capsule formulations have been tabulated in the table below.

Table12:Content Uniformity

Formulation Code	Content Uniformity
E1	97±0.23
E2	100±0.18
E3	95 ±0.25
E4	101±0.14
E5	98.4±0.84
E6	99.4±0.55
E7	98.64±0.62
E8	99.56±0.23
E9	100.5±0.15
E10	97.76±0.65

ComparativeInvitroDissolution of Innovator and Capsule Formulations

Acid stage: 0.1 N HCl, 500ml, paddle, 75rpm, 60minutes,37±0.5^{o}C.

Buffer stage: pH 6.8 phosphate buffer, 900ml, paddle, 75rpm,37±0.5^{o}C

Sampling points- 10, 20, 30, 45 and 60 minutes.

Table:13:Dissolution of Innovator &Capsule Formulation

Time(min)	Innovator	Capsule formulation
	% Drug dissolved	
10	**65**	62.5
20	**74**	72
30	**80**	78.5
45	**92**	91.5
60	**95**	95

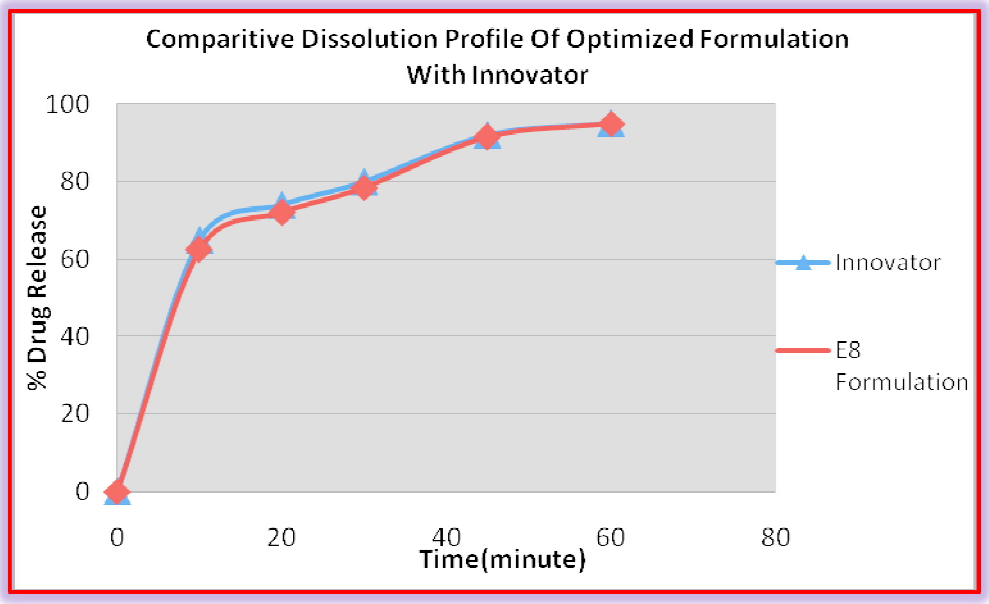


Fig. 8: Invitro Dissolution Profile of Optimized Formulation with Innovator

CHROMATOGRAMS OF OPTIMIZED FORMULATION

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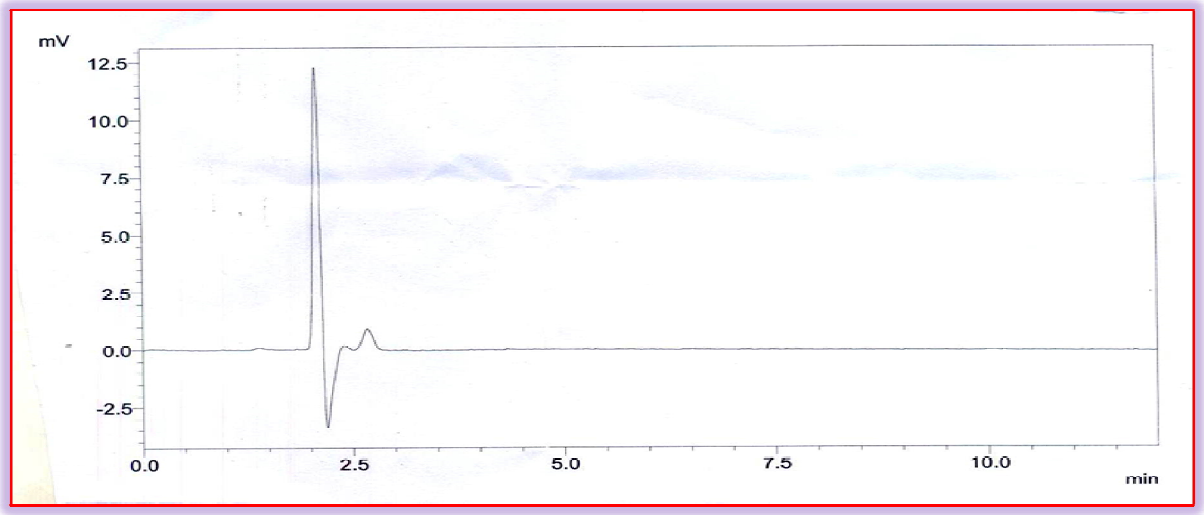

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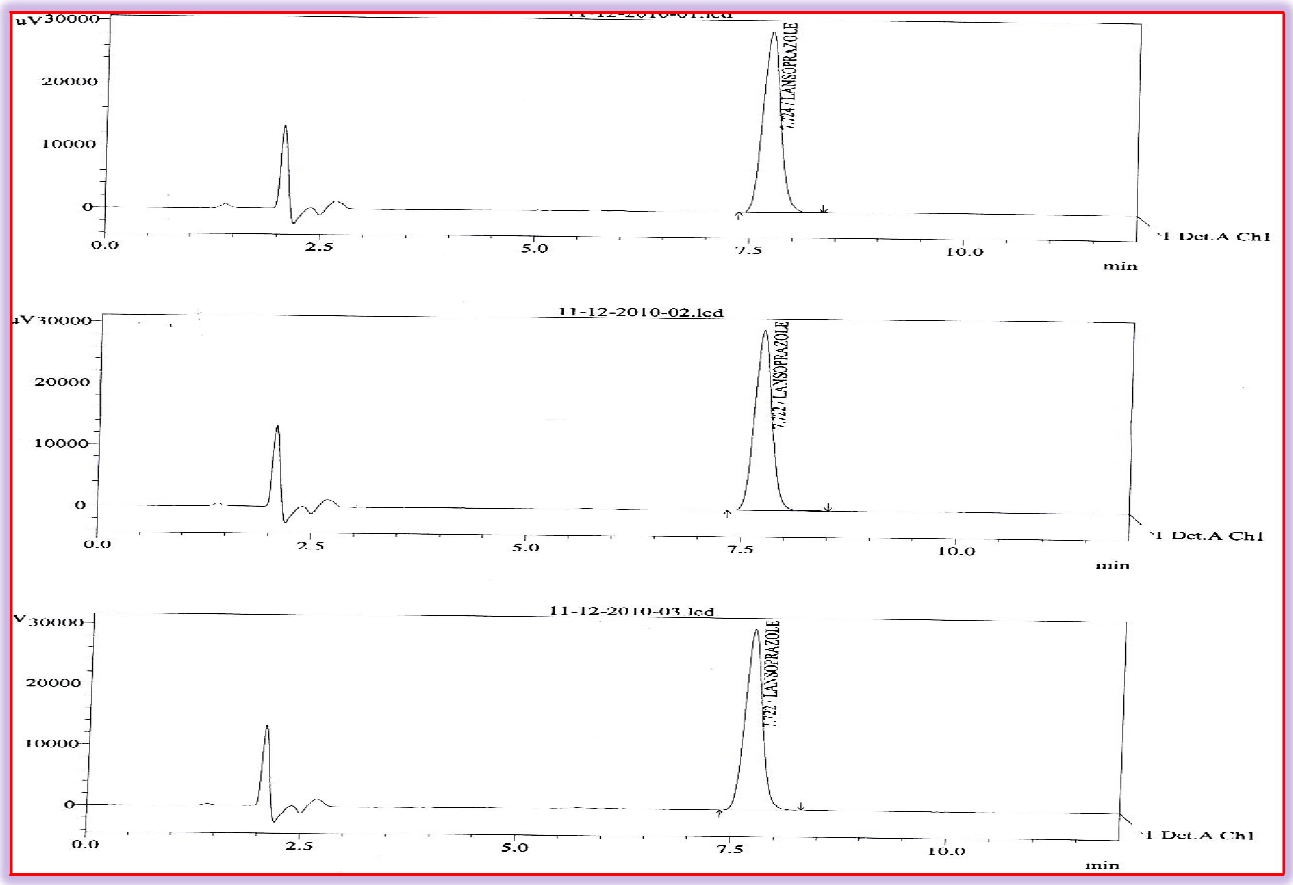
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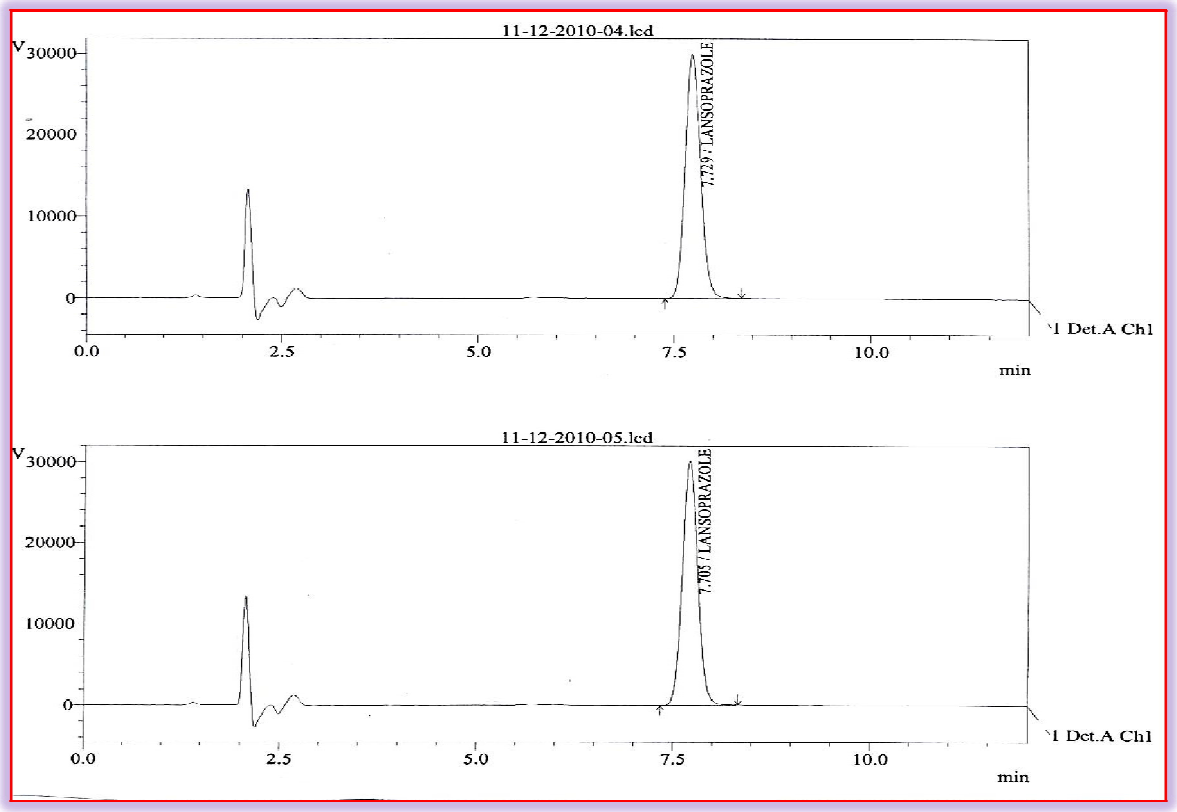

Fig. 9: Dissolution Chromatograms

SAMPLE NAME	RETENTION TIME	AREA
Standard	7.724	409739
Standard	7.722	405584
Standard	7.722	406627
Standard	7.729	405861
Standard	7.705	406544

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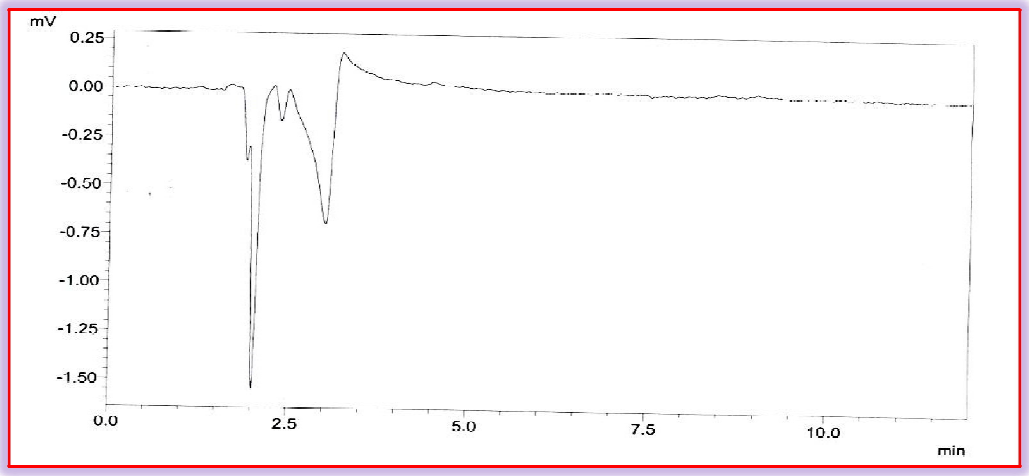

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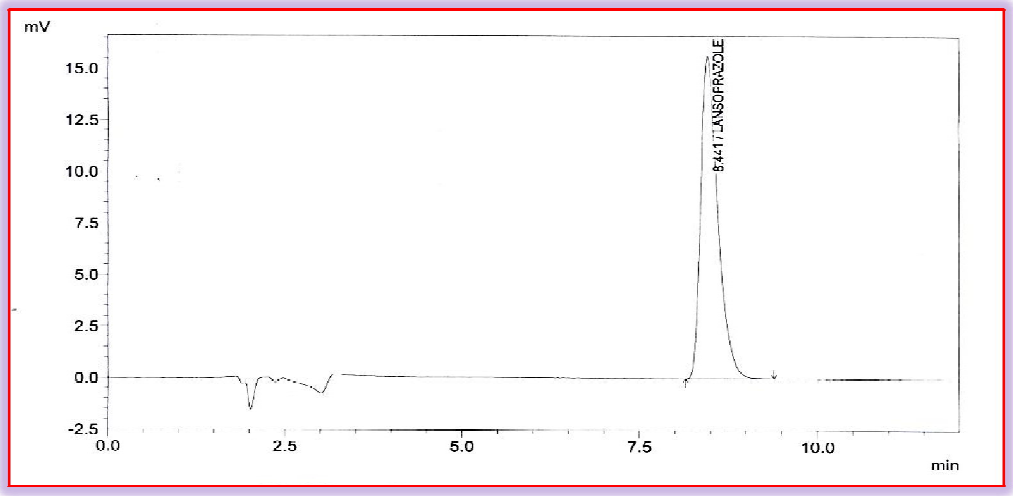

SAMPLE NAME	RETENTION TIME	AREA
Standard	8.441	259339

Fig. 10: Assay Chromatograms

DISCUSSION

The present work was an attempt to formulate and evaluate oral delayed release formulation for 30mg.It has been explored to prevent ulcers.

PELLETS

Drug Loading

Drug Loading was given to sugar spheres by using solution suspension layering technique.The six batches were developed with screened sugar spheres with binder concentrations.Then the drug coated pellets were analyzed for the amount of drug bound over the pellets.

D1 showed that the amount of the drug coated was 80%.and % yield obtained was 75%. The % yield was found to be very less and % drug content was found to be low. This may be because of povidone acting as weak binder.So further trials were planned with increased binder (povidone) concentration. D2 formulation showed 82.4% drug coating and %yield was 80%. The % drug bound in D2 formulation was considered to be better than D1, but low. Further trails were carried with increased concentration of HPC (LH 31).

D3 formulation found an increase in drug content (86.4%), and % yield (84%).But these values were low compared to marketed product.Hence to improve the % drug coating further trails were planned with a strong binder HPC (L type).The D4 formulation was found to have drug coating of 91.5% but the % yield was less. Hence to improve the process yield light $MgCO_3$ was replaced with heavy $MgCO_3$.

D5 formulation was found to have a drug coat of 99.5% and 97% yield. Process problems were also not observed during the coating process.To check the process feasibility a trial was planned by replacing HPC (L type) with HPMC.D6 formulation was found to have a drug coating of 95.3% but process related problems were found, thereby decreasing the yield to 82%. From the above trails it was concluded that HPC (L-type) (D5) was an optimized binder concentration for drug coating.

Sub coating (Barrier Coating)

Main aim of sub coating is to protect the drug coated pellets from enteric coating and environmental conditions. In the entire trials drug content was in the range of 99±2%.

In D5S1 formulation, yield was found to be low. This formulation didn't show better protection for drug coated pellets. Hence HPMC was chosen in the second trial.In D5S2 HPMC was taken for better binding and

better film formation. But the % yield was less .Hence to increase the yield and drug content starch was added.
In D5S3 the % yield was comparatively low and drug content was satisfactory. So furthertrial was planned with increased HPC concentrations.In D5S4 formulation HPC(L-type) concentration was increased for better film formation ,there by better protection was obtained to drug coated pellets with an average weight build up 17.6% w/w.Results were satisfactory .
To check the process feasibility D5S5 trial was done with increased starch concentration.Duplets were observed and the results were not satisfactory.Hence based up on results D5S4 was finalized for sub-coating.

Enteric coating
Methacrylic acid copolymer (type C) was selected as enteric coating polymer because of its flexible film formation.Optimization of enteric coating was done by comparing the parameters like assay, acid resistance and dissolution of the enteric coated pellets with the marketed product (Innovator).E1, E2, E3, E4, E5, E6, E7, E8, E9 formulations were optimized based on the above results.
In D5S1E1, D5S1E2 formulation trials 10%w/w & 15%w/w enteric polymer coating was given to the D5S1 Barrier coated pellets. The % drug release in acid was found to be 17% and 15% respectively. This may be due to less Barrier-coating which may be due to improper binding.
In D5S3E3 & D5S3E4 formulation trials 10%w/w & 15%w/w enteric polymer coating was given to the D5S3 Barrier coated pellets. The % drug release in acid was found to be 16% and 13% respectively .Enteric coated pellets color was changed; this may be due to less Barrier-coating, which may be due to improper binding.
In D5S4E5 10% EC was given to the formulation D5S4,acid release was found to be 11%.no color changes but increase in % drug release hence further trails were planned with 15%EC.In D5S4E6 15% EC was given to the formulation D4S3,acid release was found to be 5.4%.no color changes but initial % drug release was more compared to reference product, hence further trail was done by replacing TEC with PEG.
In D5S4E7 the acid release was found to be 9 %, hence it was concluded that TEC was a better plasticizer compared to PEG.In D5S4E8 17% EC was given to formulation D5S4, acid release was found to be 0.5%. Enteric coating was found to be good and results were satisfactory. A final trial was done with increased % of enteric polymer coating.
In D5S4E9 formulation 19% of enteric polymer coating was given. The acid release was found to be 0.1% and %drug release was found to be decreased when compared to reference product.Enteric coating was optimized at an average weight build up of 17%w/w.
Based on above results D5S4E8 formulation of enteric coated pellets was found to be optimum.

EVALUATION STUDIES OF CAPSULES
Enteric coated pellets of formulation E8 were filled into capsules &Evaluation tests were performed. Then the following parameters were compared with Innovator for evaluation as mentioned.
The dissolution of capsule formulation complies with Innovator as observed.The results were found be more similar with Innovator and the enteric coated formula filled into capsule was found be optimum for developing Lansoprazole delayed release capsules.

SUMMARY AND CONCLUSION
The present study was to formulate and evaluate delayed release Capsules of Lansoprazole. The formulation process was carried out in FBP by solution -suspension layering technique.
Lansoprazole is an acid labile drug; it degrades at acidic pH of stomach. To bypass stomach, the formulation has to delay the release and give the release in proximal small intestine. This can be achieved by enteric coating.
The work was carried out to delay the release of Lansoprazole by using enteric polymer Methacrylic acid copolymer (type C). The study includes preformulation of drug and excipients, formulation and evaluation, release kinetics and stability studies of capsules.The inert core material (i.e. Sugar sphere USP) was given, Drug coating, Sub coating (Barrier coating) and enteric coating.
Drug Loading was given to sugars spheres by using different binders i.e., HPMC 3cps and povidone (k-17) with different concentrations. The amount of drug bound to sugarspheres increases with an increased concentration of HPC (LH-31) (7.662% and 10.15%). Finally 10.15% w/w HPC was optimized as binder for drug coating.

Sub coating was given to drug loaded pellets to avoid direct contact with enteric coating. Sub coating was given with HPC and Corn starch combination at an average weight build up of 17.6% w/w of sub coated pellets.

Enteric coating was given to Lansoprazole pellets by Methacrylic acid copolymer type C (30% aqueous dispersion). Enteric coating was optimized at an average weight build up of 17 % w/w of enteric coated pellets and release profile was compared with Innovator. In enteric coating, plasticizer plays major role in film formation of pellets. Among TEC and PEG 6000, TEC was found to have good film forming capacity. Plasticizer concentration was optimized at 33.3% w/w of dry polymer weight.

Enteric coated pellets were evaluated for assay, acid resistance and dissolution; E8 enteric coated pellets were found to be optimum and were filled into capsules. These capsules were evaluated and the results were found to be more similar with innovator. Based on the above data, it was concluded that Lansoprazole Capsules 30mg (E8) complies with the Innovator and may be considered as an ideal formulation for developing Lansoprazole delayed release capsules 30mg.

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